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ABSTRACT

Fragile X syndrome is the most common cause of mental retardation next to Down syndrome. The syndrome is more prevalent in males because they only have one X chromosome, where the gene for fragile X is carried, while women have two X chromosomes and the normal gene can compensate for the affected chromosome. Certain physical features are associated with the syndrome, such as elongated faces and hyperextensible finger joints. Children with fragile X have IQs that decline as they become adults. Language problems affect all males with fragile X, even those that have a normal IQ. Many prepubertal males may have borderline IQs, learning disabilities, attention deficits, and hyperactivity. Primary weaknesses include arithmetic, short-term memory, and signs of autistic behavior that lasts into adulthood. Women with fragile X show milder symptoms than men, both in physical and cognitive problems. One of the main treatments for fragile X is folic acid, along with special education, language therapy, occupational therapy, and psychotherapy. Genetic counseling is very important for anyone who is aware of having or being a carrier of the fragile X syndrome. (Contains 12 references.) (JDD)

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MALE-FEMALE CHARACTERISTICS OF FRAGILE X SYNDROME

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ABSTRACT

Research from various sources were studied describing the differences in males and females with fragile X syndrome. This compilation of data shows patterns of descriptors which can be utilized in the diagnosis of fragile X. Caution is recommended, since these descriptors are also found outside of the studied subjects. Males were found to acquire the fragile X syndrome to a greater degree of severity, and more frequently, than females. Discussed in this paper are interesting genetic manipulations involving chromosome sorting, and implantation of an embryo into the uterus of women with fragile X. Longitudinal research is critically needed for future studies.

MALE-FEMALE CHARACTERISTICS OF FRAGILE X SYNDROME

One of the most perplexing, but important discoveries in modern genetics was the discovery of the fragile X syndrome. Fragile X can be seen as a break or weakness on the long arm of the chromosome, and thus is the condition under which the fragile x syndrome is identified. The syndrome effects one out of 1500 males and one out of 2500 females, and can effect more than one person within a family. Fragile X has no ethnic boundaries and can occur among all races and cultures (Nussbaum and Ledbetter, 1986).

Since the nineteenth century, researchers have observed the fact that more men than women are institutionalized for mental retardation. It was previously thought, during the nineteenth century, that the unequal ratio of men and women was due to the fact that men had more responsibilities and obligations. This assumption was accepted until 1943, when Martin and bell discovered the relationship between mental retardation and the X-link (Nussbaum and Ledbetter, 1986).

In 1969, Lubs, identified the marker X chromosome in some mentally retarded males. Unfortunately, when Lubs published his paper he received very little attention. It was not until the 70's that fragile X was considered a common genetic mechanism, and the 25% higher proportion of males was explained. Next to Down's Syndrome, Fragile X is the most common cause of mental retardation (Meryash, 1985).

The fragile X site is on the tip of the long arm of the X chromosome, and often appears loosely attached by only a strand, or it may be completely unattached. This breakdown always occurs at band xq27, and does so consistently in every fragile X case. Fragile X chromosomes can appear in 50% of the cells examined in an affected male. The frequency of the occurrence of fragile X has no relationship to the severity of the symptoms in the males tested (Meryash, 1985).

Fragile X is the most common form of "inherited" mental retardation. According to Hagerman and Sobesky, (1989) the fragile X syndrome will occur in 50% of the sons of a carrier mother, and 50% of the carrier mother's daughters will be carriers. Only 30% of the

carriers daughters will have some form of the retardation.

When the mother is retarded and has had one son with fragile X, she has a 50% chance that her second son will have the syndrome. If she should have a daughter, the chances that she would be affected is 28%. If a son should be born normal, he has a good chance of not being a carrier. If the mother is normal, she has a 38% chance of having an affected male offspring, and a 16% chance of having an affected female offspring. A male carrier will transmit the syndrome to his daughters, but most of them will be normal. The father cannot transmit the syndrome to his sons (Buird, Bornhoeft, and Kerbeshian, 1985).

The reason that fragile X is more prevalent in males is that they only have one X chromosome. The gene for the fragile X syndrome is carried on the X chromosome. If the male has the fragile X chromosome, he will normally have the characteristics of the syndrome. Women, on the other hand, receive two X chromosomes and the normal gene can compensate for the affected chromosome. In other words, one X chromosome will be inactivated (Meryash, 1985).

The predominant physical features that have been associated with men that have fragile X are long thin faces, mid-face hypoplasia (arrested development of the midface), prominent jaw, large simple ears, and macoorchidism (large testicles) (Rogers & Simensen, 1986). Around 90% of affected males will have at least one or more of these symptoms. In addition, features noted in 20 to 60% of males with fragile x are hyperextensible finger joints, flat feet, strabismus (abnormality of the eyes), pectus excavatum (funnel chest), Mitral valve prolapse, single palmer crease, and a high arched palate. They have discovered that a connective tissue abnormality explains the large ears, hyperextensible finger joints, and macroorchidism that occurs in a single syndrome.

The enlarged testicles of a fragile X male show an increase of ground substance, interstitial fibrosis, and tortuous (twisted) spermatic tubules. In these cases fertility is normal (Hagerman and Sobesky. 1989). Many men have a slightly enlarged head circumference, due to megalencephaly (large brain) and a thickened calvarium. They have found increased ventricular size through CAT

scans, possibly due to the under development of the brain (Meryash, 1985). In prepubertal males, the long narrow face is not seen, also the macroorchidism is so subtle that it is not often seen. The young males tend to have larger ears than normal in this age group (Hagerman & Sobesky, 1989).

Women have two X chromosomes, consequently the normal chromosome provides a certain amount of protection depending on which chromosome is inactivated. Women that are mildly affected commonly have slightly prominent ears. They may also have double jointed thumbs and hyperextensible finger joints. Elongated faces or prominent faces are seen in adult women and more often in older women. When using an ultra-sound method, enlarged ovaries were indicative of women with the fragile x syndrome. Although fertility is normal, some of these women have a history of premature ovarian failure and premature menopause (Hagerman & Sobesky, 1989).

Men with the fragile x syndrome express a limited range of intellectual ability from borderline to profound mental retardation (M.R.) (De La Cruz, 1985).

Boys with fragile X range in intelligence from average, to severe M.R. A study on the fact that children with fragile X have IQ's that decline as they become adults was done in 1987. To perform this study, they selected men and boys that were Caucasian and from middle to upper class families. Previous I.Q. scores were acquired and new ones were administered. They performed both cross-sectional and longitudinal studies on the subjects. It appears that as these children grow, they learn at a slower rate and they do not gain in cognitive skills at a rate consistent with their previous I.Q.. The primary element that contributes to the declining I.Q.s of males is the primary encephalopathic abnormality, because it becomes more pronounced in later childhood when children should be learning more abstract reasoning abilities, and sophisticated cognitive skills. Many other problems can have a possible effect on the declining learning abilities of these men, such as attention deficits, poor organizational skills, and hyperactivity (Lachiewicz, Gullion, Spiridigliozzi, and Aylsworth, 1987).

Most of the adult men with fragile X, that are moderately retarded, live in group homes and work in

sheltered workshops. Around 30% are severely or profoundly retarded and must be institutionalized. Language problems affect all males with fragile X syndrome, even those that have a normal I.Q. The most common problems are auditory processing, memory, sequencing, and word retrieval. Even males that are able to function at high levels have demonstrated cluttered speech, dysfluencies, rapid speech rate, frequent tangential remarks, and poor topic maintenance (Hagerman, & Sobesky, 1989).

Many prepubertal males that have borderline I.Q.'s have learning disabilities, but are not retarded. They tend to be hyperactive and have attention deficits. Hyperactivity tends to disappear in adulthood but attention problems will persevere into adulthood. They have strengths in spelling and reading, and their primary weakness is in arithmetic (Hagerman & Sobesky, 1989). Short-term memory is a problem for boys and men with fragile X. Any task that involves short term memory is a difficult problem for them (Meryash, 1985).

Research has shown that children with fragile X that live at home and attended special education classes

will function higher as adults than the older men who were institutionalized as children. Even with fragile X these men (and boys) will engage in normal social activities (Meryash, 1985).

When affected men, or boys over the age of twelve, greet someone they turn their head and body away from the person they are greeting, and avoid eye contact even with family members. Boys that are under twelve do not have the social gaze avoidance problem (Wolff, Gardner, Paccia, & Lappen, 1989). These people not only have poor eye contact, they have a history of shyness, and a high degree of difficulties with social interaction (Hagerman & Sobesky, 1989).

Many fragile X males show signs of autistic behavior that lasts into adulthood. They have unusual hand mannerisms such as hand biting and hand-flapping. As many as 16% of all fragile x males will fulfill requirements for Infantile Autism according to the DSM 111-R (American Psychiatric Association, 1987). Fragile X males show a dislike of being touched and a fascination with household objects such as vacuums, mixers, and similar items (Hagerman, & Sobesky, 1989).

Women with fragile X show milder symptoms than men,

both in physical and cognitive problems. The milder symptoms are due to the, previously discussed, protective chromosome. Research shows that around 30% of affected females have cognitive deficits, with I.Q.'s ranging from borderline to more significant retardation. The remaining 70% of women have a normal I.Q. and previously had been diagnosed as not affected by the syndrome. Further research indicates that these women tend to have specific weaknesses in math which normally requires special education in this area. They have difficulties with dyscalculia (impairment of ability to calculate math), right-left disorientation, constructional and finger agnosia (inability to distinguish between different fingers). They also suffer from an impairment of the ability to carry out a skilled activity with out paralysis, alaxia, or any other abnormality of the primary motor pathways, called dyspraxia (Hagerman, & Sobesky, 1989).

Women with fragile X have several areas of other difficulties. They have a hard time focusing and paying attention. They often jump from one idea to another when talking, which makes them feel that their thinking

is out of control. Their thinking and problem solving skills are loose and disorganized. They have a hard time explaining how they feel or what they think about their problems, or just life in general (Hagerman, & Sobesky, 1989).

Women with fragile X syndrome experience many social problems. Much like the affected men, women also have poor eye contact when greeting other people. the fragile X women is very dependent on other people and easily manipulated. They seem to have a feeling of helplessness and think that other people will reject them. Women have feelings of isolation and they have difficulty with close friendships. They have a problem with low self-esteem due, in part, to academic difficulties. Depression is a problem with the higher functioning females because they are aware of their problems and limitations (Hagerman & Sobesky, 1989).

Treatment for Fragile X

One of the main treatments for fragile X is folic acid. Studies of the treatment using folic acid have shown some patients making progress, when given high doses of folic acid (Burd, Bornhoeft, and Kerbeshian,

1986). One study group using prepubertal boys found that they improved in both intellect and behavior. They also demonstrated longer attention spans, decreased hyperactivity, decreased aggressiveness, and decreased unusual hand movements. Parents, and teachers, both noticed an improvement in the boys performance with the folic acid treatment (Rogers and Simensen, 1986).

Boys that are affected with fragile X can be treated with a multimodal approach that involves special education, language, and occupational therapy. They may be given medication that will improve attention problems, and hyperactivity. To help with emotional and behavior problems psychotherapy is utilized. Psychotherapy can be useful in helping women with learning disabilities and mild to moderate emotional dysfunction (Hagerman and Sobesky, 1989).

A major break through may have been made in a experimental study dealing with implantation of embryos for "at risk" couples. The couples used in this study were at risk of transmitting recessive X-linked diseases and all the women had previous terminations of affected fetuses. All of the couples agreed to try the

implantation method used in the study. Oocytes (female ovum) were collected and fertilized during each treatment cycle. Of these, 79% developed to the six to ten-cell stages on day three. These were biopsied and after identification of the sex, the subjects were implanted with all female embryos. The implantation worked in two of the five women. When given an ultrasound, two of the women were pregnant with dizygotic female twins. This was presumed from the development of both biopsied embryos. This will be confirmed at birth. This implies that implantation will be a viable option for families that carry genetic defects (Handyside, Kontogianni, Hardy, and Winston, 1990).

When obtaining cultured fibroblasts from two hemizygous males and a heterozygous female, Glover (1981) was able to demonstrate the marker X. This finding was able to pave the way to demonstrate the marker X from cultured amniocytes obtained from carriers of the fragile X syndrome. The problems that may occur with this finding are that normal fetuses may be aborted and affected ones may not be detected. Another problem would be that as many as 66% that show the fragile X may

be intellectually normal, so this process is still considered experimental, cited in (De La Cruz, 1985).

Genetic counseling is very important for anyone that is aware of having or being a carrier of the fragile X syndrome. In a study performed on people at risk for fragile X, in which 61% of their pregnancies were monitored, there was a 26% reduction in pregnancies. (Turner, Robinson, Lang, Van Den Berk, Colley, Goddard, Sherman, and Partington, 1992).

There are complications in counseling families with the fragile X syndrome because one-third of heterozygotes will have some sort of developmental disabilities and some will be normal (De La Cruz, 1985). To confuse the issue, at times, a single child will have fragile X with no known history of the syndrome in the family. Counseling can help families discover explanatory possibilities such as, an affected male in past generations that functioned adequately and the syndrome was not found. The mother could be from a small family without any brothers, and the grandmother could have come from the same sort of family and the syndrome could have gone undetected for several

generations. Genetic counseling can help these families not only in answering questions, but to guide them in locating assistance. The state has programs dealing with genetics, that aid in diagnosis of fragile X and also provides services for people with fragile X (Meryash, 1985). With , Goddard, Sherman, and Partington, 1992).

Aiding in the education of those with fragile X was the passing of Public law 91-142, the catalyst for school systems to become responsible for providing education for children with fragile X, as well as all handicapped individuals. The schools must provide teachers, and counselors, trained to educate children with learning disabilities and retardation.

CONCLUSION

To summarize; scientists, psychologists, physicians, counselors, special education teachers and others, are working hand in hand to educate, and counsel individuals with fragile X, both in coping in society, and in trying to scientifically eliminate the syndrome through genetic manipulation or other means. The most promising research which the author found was on this genetic sorting of

embryos, and implantation of the female, thus eliminating the fragile X in the offspring. This could, in time, greatly reduce or eliminate the incidence of fragile X. Great strides have been made in the area of education of individuals with fragile X, and studies show that they do benefit and are "more able" to cope in society with proper education, and with the care and attention of significant others.

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